TB MED 31

WAR DEPARTMENT TECHNICAL BULLETIN

SCRUB TYPHUS FEVER
(TSUTSUGAMUSHI DISEASE)

War Department, Washington 25, D. C. • • • • • • 11 April 1944

1. GENERAL.—Scrub typhus (mite-borne typhus) fever is a specific febrile disease transmitted by a mite. It clinically resembles the other rickettsial diseases and is characterized by a sudden onset with ferbrile course of approximately 2 weeks, a cutaneous eruption, and the presence of an ulcerative and necrotic lesion, called the eschar, at the site of attachment of the mite vector. Agglutinins for the OXK strain of the Proteus bacillus can be demonstrated in most cases in the patient's blood by the end of the second week of disease.

a. The disease is probably identical with tsutsugamushi disease (Japanese river fever), rural or tropical typhus of the Federated Malay States, pseudotyphus of Sumatra, and Sumatran mite fever. It is included in coastal fever and Mossman fever of North Queensland.

b. Scrub typhus has assumed military importance because of its prevalence in the Southwest Pacific Area and the China-Burma-India Theater.

2. ETIOLOGY.—The causative organism is a rickettsia (*R. orientalis*, also called *R. tsutsugamushi*). Though demonstrable with difficulty in human tissue, this rickettsia is readily transmitted to white mice by inoculation producing a fatal infection, in which the minute intra- and extra-cellular rickettsiae, frequently appearing in pairs, may be demonstrated with proper staining technique. Although the guinea pig and monkey are susceptible, infection and death of these animals is not regularly produced by certain strains of the organism.

3. GEOGRAPHICAL DISTRIBUTION. — The disease has a wide geographical distribution in the Asiatic-Pacific Area, extending from Japan down along Indo-China through the Federated Malay States out into the East Indies, New Guinea, North Queensland, and the islands of the Bismarck archipelago.

a. Although the disease was originally thought to be confined to Japan, scrub typhus has been found in the Nansei Islands, Formosa, the Pescadores, Korea, Malaya, Ceylon, Maldive Islands, Sumatra, Java, Borneo, Australia (North Queensland), New Guinea, islands in the Solomons group, and areas of French Indo-China, China, India, and Burma.

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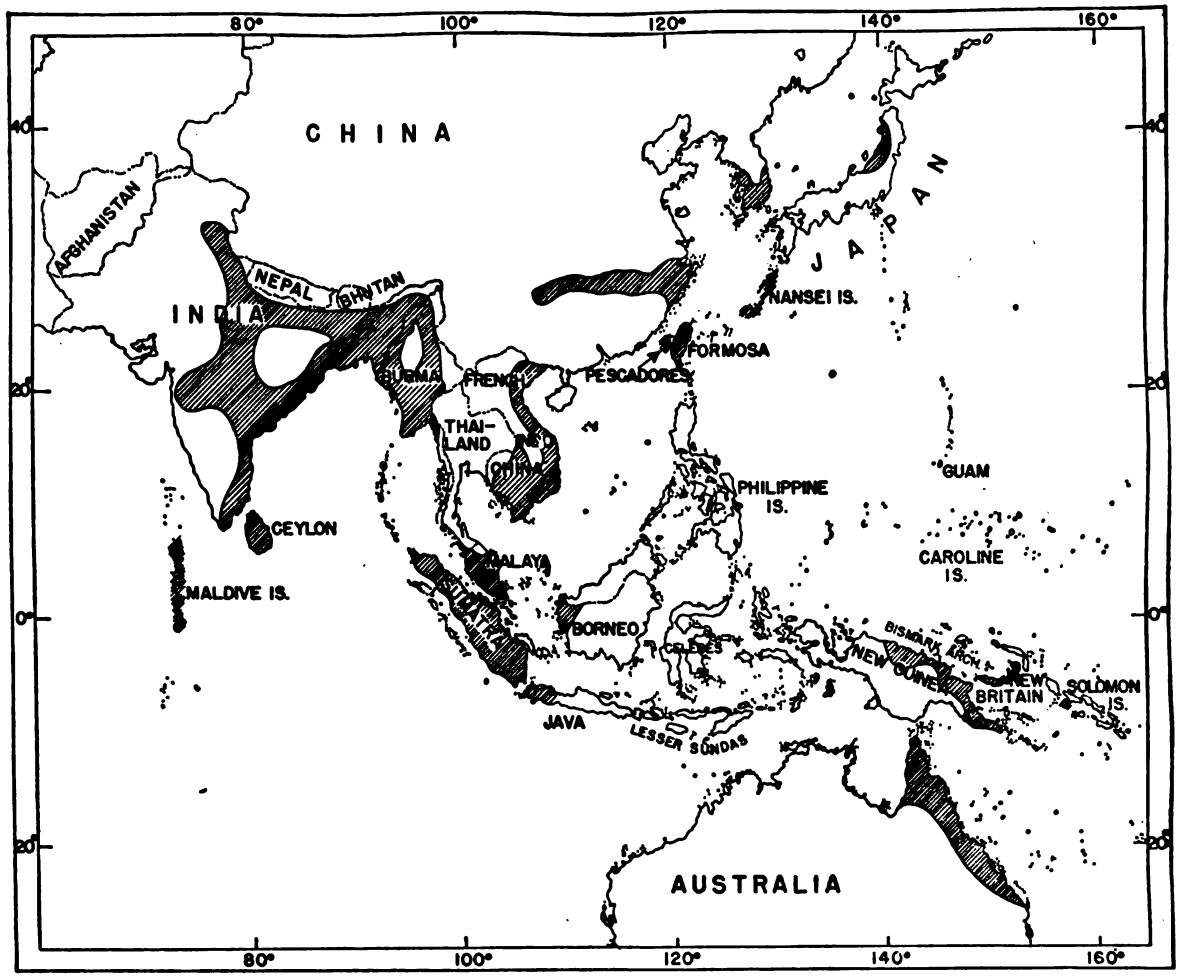

FIGURE 1.—Geographical distribution of scrub typhus.

b. It is highly probable that scrub typhus will be found in many areas of China, Burma, the East Indies, and in islands of the Bismark archipelago where the disease has not been described previously. Medical officers in these areas, therefore, should be constantly on the lookout for scrub typhus, and consider this disease in the differential diagnosis of fevers of uncertain etiology in order that prompt preventive measures may be instituted upon the recognition of its occurrence.

4. TRANSMISSION.—Scrub typhus is transmitted to man by the larval form of a mite of the genus Trombicula, family Trombidiidae, order Acarina.

a. The Trombidiidae, known popularly as "harvest mites," "red bugs," or "chiggers" fall into the class Arachnida, and are distinguished from the Insecta by the presence of four pairs of ambulatory appendages in the adult. In their development, they pass through four main stages—egg, larva, nymph, and adult. The six-legged larval forms are parasitic on vertebrates and must have a blood (serum) meal from such a host prior to metamorphosis to the nymph stage, following which they become adults. In the last two stages, the mites feed on plants and are thus not parasitic on man or animals. The adults lay their eggs on the ground, whereupon a new larval generation hatches out, and the cycle is repeated.

b. The six-legged larval form of the mite which attacks man is almost microscopic in size varying from 0.15 to 0.4 mm (0.006–0.016 inch).

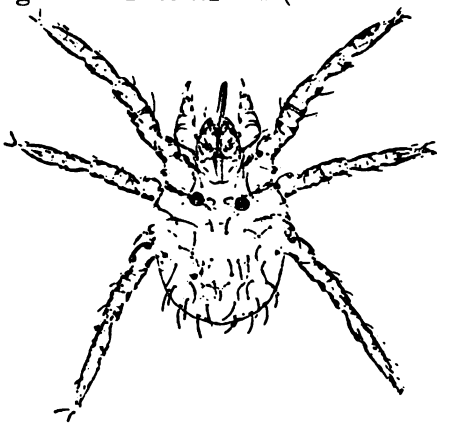

FIGURE 2.—Photomicrograph of *Schongastia minor*. X45

It is usually red or reddish in color, and the body and legs are covered with fine hairs, the number, location, and length of which vary according to the species. The larvae attach themselves to the skin by means of their hooked chelicerae (mouth parts) for feeding. Some species, such as *Trombicula irritans* in North America and *Schongastia minor* in New Guinea cause a severe dermatitis with intense itching ("harvest itch" or "scrub itch").

c. Larval mites become infected while obtaining a blood (serum) meal from a vertebrate host that is infected with scrub typhus. This one meal is all that is required for the metamorphosis of the mite, and it is believed that the infection it acquires is perpetuated in subsequent generations.

d. There are numerous species of mites and, with the exception of *Trombicula akamushi* in Japan, the mite vector of the disease in other areas has not been definitely established. Evidence suggests that *Trombicula deliensis* and *Trombicula walchi* may transmit scrub typhus. It is highly probable that the species of mites causing "scrub itch" do not act as vectors since little, if any, correlation has been noted between the incidence of scrub typhus and "scrub itch".

e. Even less definite information is available concerning the animal reservoir of scrub typhus. It is probable that field mice, rats, or other animals, such as the bandicoot, serve as the natural pool of infection in various areas. These animals are the natural hosts of mites; man serves only as an accidental host.

5. EPIDEMIOLOGY.—*a.* In general, transmission of scrub typhus is not necessarily limited by season in the tropics, but is rather associated with the arrival of troops or groups of workers into endemic areas, or with local agricultural pursuits which necessitate the entry of workers into known endemic foci. In Japan and Formosa, however, definite seasonal incidence has been demonstrated. Investigation has shown that the risk of infection is maximal:
(1) During the first 4 to 6 weeks after an organization has occupied a camp site which has not been previously used.
(2) When an organization engaged in combat is constantly moving into and occupying new areas.

b. The disease is focally distributed and, although present knowledge does not permit a distinction between those localities in which the danger of infection is great and those in which there is little or no risk, the danger of infection does appear to be associated principally with the following types of terrain, the common factor probably being conditions that produce a moist, damp soil favorable to the growth and activity of the specific mites which act as the vector of scrub typhus:
(1) In Japan, in fields along the course of rivers subject to flood conditions.
(2) In Malaya, India, China, Burma, Sumatra, and Australia, in areas in which there is a thick luxuriant growth of "scrub" (a dense, low growth of dwarf or stunted trees, or shrubs, or an admixture of these).
(3) In New Guinea, in areas in which there are large "kunai grass" fields bordered by the jungle.

6. PATHOLOGY.—Scrub typhus is basically a disseminated, focal vasculitis and perivasculitis of the smaller blood vessels. The vessels principally involved are those of the skin, lungs, heart, and brain.

a. Although endovasculitis, thrombosis, and hemorrhage may occur, these are conspicuously less marked than in European (epidemic) ty-

phus. The vascular lesions consist of perivascular accumulations of monocytes, plasma cells, and lymphocytes, with moderate focal edema, In severe lesions, necrosis of adjacent tissue cells may occur, especially in the myocardium and brain nodules.

b. The vasculitis and perivasculitis in the lungs causes a true rickettsial pneumonia with swelling of the alveolar walls and exudate of large mononuclear cells, plasma cells, and lymphocytes into adjacent alveoli. Serum and red blood cells are also often present in the alveolar spaces. Bronchial and bronchiolar epithelium are intact. The picture as described may be complicated with the findings of a terminal bronchopneumonia.

c. In severe vasculitis of the myocardial vessels, there may be infiltration of the interstitial tissue with mononuclear cells, edema, and, rarely, even small areas of focal necrosis of muscle fibers.

d. The brain is frequently the seat of a focal perivascular reaction characterized by proliferation of glial cells and infiltration with large mononuclear cells.

e. The spleen shows enlargement with accumulations of large mononuclear cells, plasma cells, and lymphocytes in the sinusoids. There is a generalized enlargement of the lymph nodes, and the regional nodes draining the site of the eschar are sometimes more conspicuously involved than other lymph nodes and show necrosis upon section. Surrounding these areas of necrosis are accumulations of large mononuclear cells.

7. CLINICAL FEATURES.—Following an incubation period of from 10 to 18 days, the onset of the disease is sudden and is associated with headache, chilliness, and fever. During the first week, the fever rises in a stepwise fashion, reaching from 102° F. to 105° F., by the beginning of the second week of disease and, ordinarily, remaining elevated until the beginning of the third week, at which time it subsidies by lysis. There may be wide swings in the temperature curve accompanied by profuse sweating, particularly if aspirin is administered. Headache may increase in intensity and become quite severe. There is injection of the bulbar conjunctivae. The patient becomes apathetic, and in severe cases, a muttering, restless delirium is observed. Anorexia is common.

a. Eschar.—A small necrotic ulcer, called the eschar, is frequently seen at the former site of attachment of the infected mite. This primary lesions, which is from 2 to 10 mm in size, consists of a round or oval ulcer surrounded by a slightly elevated pink areola and covered centrally with a black scab. In moist surface areas of the body such as the axilla, scrotum, perineum, and occasionally elsewhere, the black central scab is lacking, the lesion appearing as a punched-out shallow ulcer with rolled edges and with a flat greyish or greenish-yellow base surrounded by the usual pink areola. It is located indiscriminately all over the body with the possible exception of the scalp, palms, and soles. Occasionally, there may be two or three eschars. The eschar is present at admission and usually persists during the active period of illness. The lesion should be searched for with great care since it may be present on parts of the body not subjected to routine examination.

b. Rash.—A characteristic skin eruption, ordinarily consisting of slightly raised dull or raspberry red macules, appears on the trunk from the fifth to the eighth day. This rash ordinarily fades within several days, but at times may be of an evanescent character, appearing and disappearing the same day. The distribution of the rash may extend to the arms and legs and at times assume a maculopapular character. An enanthem on the soft palate is occasionally seen.

c. Reticulo-endothelial system.—(1) An almost constant finding is generalized lymphadenitis of variable degree which appears early in the disease and persists for the duration of the active stage. The regional lymph nodes draining the eschar are likely to be more enlarged than elsewhere and somewhat tender.

(2) A slightly enlarged, tender spleen appearing at the end of the first week is common, but the value of this finding as a diagnostic point is questionable in view of the high incidence of splenomegaly due to malaria in the regions in which scrub typhus is endemic.

. *Central nervous system.*—In addition to usual apathy and headache commonly seen, fusion, disorientation, muscular twitching, tagmus, and even convulsions may be ob-ved. Variable degrees of deafness, ordi-ily transient, have been reported.

. *Respiratory system.*—Cough early in the ease is frequent, and physical signs of pneu-nitis, such as fine and medium moist rales r the lower lobes, are present. In severe es, these signs may extend into the upper es with scattered sibilant rales, diminished ath sounds at the bases, and tachypnoea with ndency toward hyperpnea and cyanosis, pre-nably anoxic in nature. Frank dullness and ular breathing are absent, but these may be ind when a secondary bacterial pneumonia velops as a complication.

f. Circulatory system.—Variable degrees of rocarditis may be present. In severe cases, hycardia, hypotension, and signs of pulmon-y congestion may be present. Although these gns could be due to damage of the myocardium the left ventricle, other factors, such as peri-eral vasodilatation and pneumonitis, must be ken into account.

8. LABORATORY FINDINGS.—*a. Hema-logical.*—Although there is no specific blood cture in scrub typhus, the leukocyte count either below or within the normal range ring the first week. Severe cases with umonitis frequently show a leukocytosis up 12,000 to 15,000 during the second and ird weeks. In cases progressing favor-ly, there is usually a relative and absolute crease in the lymphocytes during the second d third weeks. Anemia is rarely observed.

b. Serological.—The presence of agglutinins r the Proteus OXK bacillus can usually be monstrated in the patient's serum by the end f the second week. With a properly standard-ed and controlled antigen, a titre of 1 : 160 may e regarded as significant, although a diagnos-c OXK agglutination test is best interpreted y a rise and fall in titre, since values of less han 1 : 160 have been not uncommonly observed n scrub typhus. A series of agglutination tests s of far greater value in interpretation than a single titre of 1 : 160 or over. Even a negative agglutination test does not exclude scrub typhus if all other characteristic features are present. Indeed, rickettsiae have been recovered from the patient's blood in some such cases. The agglutination titre usually reaches its peak during the third week, begins to decline rapidly in convalescence about the fourth week, and becomes negative several weeks later.

c. Blood chemistry.—In occasional cases, the plasma proteins may be slightly lowered during the second and third weeks. There is a frequent fall and, at times, even reversal of the albumin-globulin ratio due to the decrease in albumin content of the plasma along with an accompanying increase of the proteins in the globulin fraction. A conspicuous fall in fibrinogen concentration of the plasma with progress of the disease into the second and third weeks indicates impairment of hepatic function. In most cases, a definite hypochloremia develops during the second and third weeks, probably due to inadequate salt intake and excessive sweating. The icteric index may be elevated in occasional cases; in such instances, the van den Bergh reaction is direct.

d. Recovery of rickettsia.—Isolation of the causative rickettsia from the patient's blood in the early stage of the disease is relatively simple. A small portion of blood clot, obtained aseptically, is ground up in a mortar with sterile sand and normal saline; after spinning down the sand and debris in a centrifuge at low speed, 0.3 cc. of the supernatant fluid is injected intraperitoneally into white mice. The infected mice die in from 10 to 16 days. Giemsa-stained smears obtained by scraping the serous membranes of the peritoneal cavity reveal the presence of minute intra- and extra-cellular diplococcal bodies which are the causative rickettsia. The smear should be fixed in methyl alcohol prior to staining.

9. DIFFERENTIAL DIAGNOSIS. — Scrub typhus is to be differentiated from the other members of the typhus group—epidemic and murine typhus, and spotted fever—and, in the early stage, from such diseases as dengue, malaria, and infectious hepatitis which may be commonly found in endemic scrub typhus areas.

The characteristic primary lesion and Weil-Felix reaction (positive OXK, negative OX 19 and OX 2 agglutinations) serve to separate scrub typhus from the other members of the typhus group. In the case of dengue, malaria, and infectious hepatitis, early differential diagnosis depends upon finding an eschar since the other early clinical features, such as headache, conjunctival injection, rising fever, relative bradycardia, and absence of leukocytosis are found in these infections. The skin eruption, appearing on the fifth to eighth day, may be of diagnostic value but, again, sufficiently similar rashes may be seen in these other diseases. Final diagnosis is confirmed by a diagnostic OXK agglutinin test. Recovery of the causative rickettsia from the blood by inoculation of white mice, and its identification, proves the diagnosis.

10. PROGNOSIS.—*a.* The case fatality rate in the Armed Forces has ranged between 2 and 10 percent, according to figures available from American and Australian sources. Differences between mortality rates in various units is dependent on a number of variable factors, such as age and physical condition of the patient, stage of the disease when admitted to the hospital, method of and time required for evacuation, and the coexistence of other diseases, such as dysentery and malaria. The mortality rate rises sharply after the age of forty.

b. Although not invariably so, the presence of one of the following signs is a bad omen; a combination of them indicates a poor prognosis:
(1) Increasing pulse rate, particularly if the rate is out of proportion to the temperature.
(2) Onset of muscular twitching, convulsions, and coma.
(3) Increasing leukocytosis with relative and absolute decrease in lymphocytes.

11. TREATMENT.—There is no specific treatment of established value. Neither the sulfonamide drugs nor penicillin has any effect on the course of the disease, and these drugs should not be used unless proved secondary bacterial infections, known to respond to these chemotherapeutic drugs, develop during the course of illness.

a. The most important aspect of treatment is that of good nursing care. Complete bed rest, avoidance of overexertion, frequent small feedings of food (by the nurse, in cases of severely ill patients), adequate fluid intake, and alcohol sponges for high fever should be stressed in such care.

b. From 6 to 8 grams of salt a day should be administered in hot climates, preferably by mouth or by hypodermoclysis. Intravenous fluid, if required, should be given slowly and in small amounts. Parenteral saline solutions may include glucose if necessary for nourishment.

c. A diet containing 3,000–3,500 calories daily, or more, should be provided during convalescence until lost weight has been regained. A liberal protein intake should be included in the diet. It is desirable to supplement the diet with polyvitamin tablets.

d. Symptomatic drug therapy should not be overdone. Aspirin for headache may cause violent swings of temperature and profuse sweating; its use, therefore, should be avoided. Sedatives should be used judiciously as patients are apathetic and need little sedation in general.

e. When patients with pulmonary complication become cyanotic, oxygen is indicated.

f. Digitalis is not indicated in acute myocarditis and its use, therefore, should be avoided unless there is convincing evidence of congestive heart failure.

g. The use of intravenous plasma should be limited to those cases having a proved hypoproteinemia sufficiently severe to threaten the development of generalized edema.

h. No specific treatment of the primary lesion in indicated. It should not be excised.

i. The period of convalescent treatment should be based upon the severity of the individual case. In the mild cases, patients should be able to return to duty 4 to 6 weeks after the temperature returns to normal. Convalescence should be prolonged in the severe cases, and may extend into the third and fourth month in some instances.

12. PREVENTION.—There is no protective vaccine against scrub typhus. Based upon present knowledge, the following measures should be employed in decreasing the risk of infection:

a. Locations which are to be used as new camp sites should be prepared as fully as possible

before the arrival of a new unit, employing native labor whenever it is available. All grass and scrub should be cut level with the ground, and, after drying, collected and burned or hauled away. It is highly desirable to burn over the camp area with a power oil sprayer or flame thrower. Underbrush in adjacent jungle strips should be cleared out in a similar manner.

b. Sleeping on the ground should be avoided. When practicable, cots or other structures should be provided to keep the bedding from contact with the ground.

c. At the earliest time after exposure, troops should be instructed to bathe with thorough soaping and scrubbing of the skin with a rough cloth.

d. Impregnation of clothes with antimite fluids will serve as a satisfactory method of individual control. Such measures are particularly applicable to personnel in combat areas or to those working in known endemic foci.

(1) *Antimite fluids.*—Based upon present knowledge, dimethyl and dibutyl phthallates are the most effective antimite fluids. The present QM standard insect repellent containing dimethylphthallate, Indalone, and Formula 612 may be used when supplies of the former fluids are not available.

(2) *Hand impregnation.*—Both hands are smeared lightly with the antimite fluid, and the fluid is applied to the clothing by rubbing or smearing the hands on the cloth. This process of smearing should be repeated two or three times, using a total of about 1 ounce of fluid during the entire operation. The following parts of the uniform, in addition to the entire surface of the socks, should be impregnated: trouser legs from bottom to knee, waist of the trousers, and the waist, collar, cuffs, and front of the shirt.

(3) *Sprayer impregnation.*—Large numbers of socks and uniforms can be rapidly and efficiently impregnated by spraying with antimite fluids. Between 1 and 2 ounces are required to impregnate a coverall or shirt and trousers. It is important that a "wet" or large droplet type of sprayer be used since "fog" or fine droplet sprayers will give a mist of the fluid which may be dissipated before it actually reaches the cloth.

(4) Trouser legs should be tucked inside the socks. Although it is desirable that leggings or high boots be worn, it is not necessary that these be impregnated with antimite fluid.

(5) Clothing prepared in the manner described above will be effective in repelling or killing mites for a week or longer, provided the antimite fluid is not washed out. Although it is definitely established that repellent qualities may be retained by the uniform after it has been soaked by rain, it is questionable as to whether or not these qualities are retained after the uniform has been washed with soap and water. Until this specific point is clarified, all clothing should be reimpregnated after laundering.

[A. G. 300.5 (4 Apr. 44).]

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